REMARKS

This document is filed in reply to the Office Action dated December 23, 2003 ("Office Action"). Applicants have cancelled claims 14, 15, 17, and 18 without prejudice. At the Examiner's suggestion, Applicants have amended claims 24-27 to recite the phrase "isolated." Support for the phrase can be found at, e.g., page 10 and page 11, line 3. Applicants have also amended claims 24-27 to specify that a polypeptide encoded by each claimed nucleic acid has no toxicity. Support for the amendment can be found at, e.g., page 1, line 18 of the Specification. No new matter has been introduced

Claims 24-27 are pending. Reconsideration of this application is requested in view of the following remarks:

Rejection under 35 U.S.C. § 101

The Examiner rejected all pending claims for directing to non-statutory subject matter. In view of the above amendments, Applicants request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 14, 15, 17, 18, and 24 for lack of novelty on various grounds. Applicants respectfully traverse:

I

The Examiner maintained the rejection against claims 14, 15, 17, and 18 for being anticipated by one or both of U.S. patent 6,140,066 and Hickey et al. (WO 97/15325; "Hickey"). See the Office Action, page 3, lines 4-8 and page 4, lines 12-15. Applicants have cancelled these claims, rendering this rejection moot.

II

The Examiner rejected claims 14 and 24 for being anticipated by Gray (PNAS 81, 2645-2649, 1984; "Gray") as evidenced by Covacci et al. (WO 93/18150; "Covacci"). See the Office Action, page 6, lines 2-3 and lines 28-29. Applicants have cancelled claim 14 and address claim 24 below.

Claim 24, as amended, covers an isolated nucleic acid encoding a polypeptide that contains a *Pseudomonas* exotoxin A receptor binding domain and at least two copies of an antigenic peptide sequence, the polypeptide having no toxicity.

Gray teaches a nucleic acid encoding a full-length *Pseudomonas aeruginosa* exotoxin A (ETA). According to the Examiner, this ETA contains (i) an amino region (residues 1-252) that is identical to the receptor binding domain recited in claim 24, and (ii) two ala-ala-gly-glu repeats (at position 375-378 and 523-526) that are antigenic. As such, she concluded that Gray teaches the claimed nucleic acid.

Applicants disagree. Note that the ETA taught in Gray is a full-length exotoxin protein. It is toxic since it contains domains responsible for toxicity, such as the ADP-ribosyltransferase domain. See page 2645, column 1, the penultimate paragraph.[1] In contrast, the polypeptide recited in claim 24 only contains the receptor binding domain of a *Pseudomonas* exotoxin A and is free of other *Pseudomonas* exotoxin domains. As a result, it has no toxicity and therefore differs from that taught in Gray. Thus, the nucleic acid of claim 24, which encodes the polypeptide, is novel over Gray.

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 14, 15, 17, 18, and 24-27 for obviousness. Applicants have cancelled claims 14, 15, 17, and 18, and will only discuss the pending claims 24-27.

Claims 24-27 each are drawn to a nucleic acid encoding a fusion polypeptide that contains (1) the receptor binding domain of a *Pseudomonas* exotoxin A, excluding sequences encoding any non-receptor binding domains of the *Pseudomonas* exotoxin A, and (2) an antigenic sequence. The receptor binding domain serves as an immunogenic carrier for the antigenic sequence.

It is the Examiner's position that claims 24-27 are obvious over Hickey in view of Hwang et al. J. Biol. Chem. 264: 2379-2384, 1989 ("Hwang I") or U.S. Patent 6,387,684 to

[1] In the paragraph, Gray teaches that ETA ADP-ribosyltransferase domain has toxicity. More specifically, "ETA inhibits protein synthesis in eukaryotic cells by catalyzing the transfer of the ADP ribosyl moiety of oxidized NAD onto elongation factor 2 (EF-2)." In addition, Hickey teaches decreasing ETA toxicity by deleting the ADP-ribosyltransferase domain, corroborating the toxicity of this domain. See, page 10, lines 1-4.

Hwang et al. (" Hwang II") and U.S. Patent 4,892,827 to Pastan et al. ("Pastan"). See the Office Action, page 9, the last paragraph.

Among the four references, Hwang II "is used ... since it qualified as prior art under 35 U.S.C. § 102(e) and ... is not disqualified as art under 35 U.S.C. § 103." See the Office Action, page 10, lines 1-2. Applicants disagree.

It appears to be the Examiner's position that, as the inventors named in Hwang II (i.e., Jaulang Hwang, Cho-Fat Hui. and Czong-Yueh Chen) differ from those named in this application (i.e., Jaulang Hwang, Chia-Tse Hsu, and Chun-Jen Ting), Hwang II is "a patent granted on an application for patent by another" under 102(e), even though this patent and the application share one joint inventor, i.e., Jaulang Hwang.

In this connection, Applicants would like to bring to the Examiner's attention that

> "the fact an application has named a different inventive entity than a patent does not necessarily make that patent prior art. ...[e]ven though an application and a patent have been conceived by different inventive entities, if they share one or more persons as joint inventors, the 35 U.S.C. § 102(e) exclusion for a patent is not necessarily satisfied. ... if the invention in the '313 patent [here, the application] is fully disclosed in the '712 [here, Hwang II] patent, this invention had to be invented before the filing date of the [here, Hwang II] patent and the latter cannot be 102(e) prior art to the '313 patent [here, the application]. *In re Applied Materials, Inc. v. Gemini Research Corp.*, 835, F2d 279 (Fed Cir. 1987)"

Here, although the application and Hwang II "share one joint inventor, the 35 U.S.C. § 102(e) exclusion for a patent is not [ ] satisfied." Indeed, Hwang II teaches a nucleic acid encoding a polypeptide having (1) the receptor binding domain of a *Pseudomonas* exotoxin A and (2) one or more fragments of topoisomerase I (which, at least 400 amino acid in length,[2] is clearly antigenic). As each fragment can contain identical sequence, Hwang II fully discloses the nucleic acid of claims 24-27. Since "the invention in [the application] is fully disclosed in the [Hwang II] patent, this invention had to be invented before the filing date of the [Hwang II] patent and the latter cannot be § 102(e) prior art to the [application]." In view of the above

[2] See, e.g., claim 1 of Hwang II.

remarks, Applicants submit that Hwang II is not qualified as 102(e) prior art and therefore will only discuss the other three references relied on by the Examiner.

Hickey teaches producing a GnRH-*Pseudomonas* exotoxin hybrid protein using recombinant DNA technology. The hybrid protein may include two tandem repeats of GnRH. The "preferred *Pseudomonas* exotoxin variants are [those] having decreased toxicity, ... wherein the binding or the ADP ribosylating activity has been ... [deleted], or ...having amino acids 1-252 (domain Ia) deleted." See, e.g., the paragraph bridging pages 9 and 10. As correctly pointed out by the Examiner, a Hickey hybrid protein can "[retain] the receptor binding domain." Nonetheless, Hickey does not teach or suggest a fusion polypeptide having the receptor binding domain of a *Pseudomonas* exotoxin A and excluding any non-receptor binding domains of the *Pseudomonas* exotoxin A, as recited in claims 24-27.

Pastan teaches recombinant toxins that target and kill specific cells. See column 1, lines 5-24. Referring to column 6, lines 30, 34, and 36-43, the Examiner stated that Pastan teaches a fusion protein of *Pseudomonas* exotoxin A. Applicants note that this fusion protein includes α-TGF or IL-2 sequence (to bind to specific cells) and a *Pseudomonas* exotoxin sequence encoded by plasmid pJH8 (to kill the cells). The pJH8-encoded sequence contains amino acids 253-613 of *Pseudomonas* exotoxin A, which includes all non-receptor binding domains. See column 6, lines 57-58. Clearly, this part of Pastan teaches away from the fusion polypeptide recited in claims 24-27, which excludes any non-receptor binding domains of *Pseudomonas* exotoxin A. Indeed, to the extent that Pastan teaches targeting and killing specific cells, it further leads away from the polypeptide recited in claims 24-27. More specifically, the claimed polypeptide would fail to kill target cells since it has no toxicity. Note that claims 24-27 specifically recite "no toxicity."

The Examiner also referred to a passage of Pastan (i.e., column 1, lines 15-18 and column 6, lines 60-61), which discloses plasmid pJH14 encoding the *Pseudomonas* exotoxin receptor binding domain. It appears to be the Examiner's position that Pastan teaches a fusion protein containing this domain. Applicants would like to point out that Pastan teaches making and using "protein [having] domain I alone" in this regard. See column 1, lines 15-18. In other words, this

protein is not a fusion protein required in claims 24-27. For the above reasons, Pastan does not rectify the defects of Hickey.

Hwang I teaches that domain Ia can be used as an antigen for producing vaccines against *Pseudomonas* exotoxin. It does not teach or suggest fusing it to another sequnce, as requied in claims 24-27.

Thus, Hickey, Hwang I, and Pastan, alone or combined, would not have taught or suggeted the nucleic acids of claims 24-27. In view of the reasons set forth above, Applicants submit that claims 24-27 are non-obvious over the three references cited by the Examiner, and the rejection should be withdrawn.

CONCLUSION

Applicants submit that grounds for the rejections asserted by the Examiner have been overcome, and that claims, as pending, define statutory subject matter that is novel and non-obvious. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

Enclosed is a $55 check for the Petition for One Month Extension of Time fee. Please apply any other charges to deposit account 06-1050, referencing the attorney docket 08919-022001.

Respectfully submitted,

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